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REMARKS

A. Allowable claims

Applicants appreciate the indication that claim 50 would be allowable if re-written in independent form. New claim 69 is similarly limited and should be allowable for the same reason that claim 50 is allowable.

B. Anticipation based on Cousens (U.S. 4,751,180)

All claims except claims 50, 60, 61 and 69 are subject to an anticipation rejection based on Cousens (U.S. 4,751,180).

1. Areas of agreement

After protracted prosecution, Applicants and the Examiner agree on several points and it is useful to review those points of agreement.

Both the Examiner and the Applicants agree that the Examiner may not cite as prior art information first presented in the Cousens CIP application (USSN 06/845,737), which was filed after Applicants made their invention (see the Declaration under 37 CFR §1.131 filed October 7, 1992 in the Applicants' parent '070 application). It simply is improper to cite U.S. 4,751,180 as prior art.

Applicants have not made an attempt to predate the Cousens parent application (USSN 06/717,209, filed March 28, 1985) and, for purposes of this response only, Applicants agree that parent application was filed before their invention date.

Applicants agree that, if the Examiner is entitled to rely on the content of the '209 patent application (a legal point they do not concede), then Applicants are not entitled to claims that cover either of the Cousens prior art fusion peptides described below that are disclosed in the '209 application. There is a dispute detailed below about whether the Examiner is entitled to rely on the '209 application as filed as prior art under 35 U.S.C. §102(e). If the Examiner is not entitled to rely on the content of the '209 patent application, there is agreement that the anticipation rejection must be withdrawn. There is also a dispute about whether Applicants' claims would cover those fusion peptides.

Limited to the Cousens parent ('209) application, the Examiner must take (and has taken) the position that two specific fusion proteins disclosed in the '209 application as filed ***inherently*** satisfy certain claim limitations even though the '209 application does not explicitly disclose that the fusion proteins satisfy those claim limitations. Those fusion proteins are designated GAP_P M BCA5 KRSTS PYK PYK_t ("pYPKI2") and GAP_P M BCA5 KR$(ST)_2$S SOD GAP_t ("pYSI2"), and they are described at page 15 of the '209 application as filed. For simplicity, we will refer to these two peptides as "the prior art Cousens fusion peptides".

There is also agreement that the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings in the applied art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990), cited at page 4, lines 6-10 of paper 31. Once the Examiner has done so, the applicant may submit rebuttal evidence or reasoning.

2. *Issues*

Two key issues remain.

- Is the Examiner entitled to rely on the content of the '209 priority application, which itself did not issue as a patent, under 35 U.S.C. §102(e)?
- If so, has the Examiner provided a basis in fact and/or technical reasoning to reasonably support the determination that the Cousens fusion peptides inherently possess the following feature specified in claim 47. In other words, has the Examiner provided adequate reasoning to support the conclusion that the fusion peptides include (in the words of claim 47),

> "...at least two amino acids defining a secondary structure which promote cleavage by said cleavage agents at said cleavage site."?

a. Is the Examiner entitled to rely on the content of the '209 priority application, which itself did not issue as a patent?

MPEP 2136.03 Section IV provides for a brief description of case law concerning 102(e) CIP rejections. In order to carry back the 35 U.S.C 102(e) critical date of the U.S. patent reference to the filing date of a parent application, the parent application must support the

invention claimed in the issued patent as required by 35 USC 112 first paragraph. The MPEP references *In re Wertheim*, 646 F.2d 527, 537, 209 USPQ 554, 564 (CCPA1981). The principals are clear. Disclosure added after Applicants' invention may never be relied on as prior art. Disclosure in an abandoned parent application may be relied on ONLY if that disclosure supports the invention claimed in the issued patent.

The Examiner does not follow the principles required by both the MPEP and the holding in *Wertheim*. Instead, the Examiner creates an entirely new standard: Does the abandoned parent application contain any patentable subject matter at all? The Examiner casts about the Cousens et al. '209 abandoned parent application focusing on the two fusion peptides that Cousens et al. chose not to cover in detailed claims in their CIP patent. The Examiner analyzes hypothetical claims to the two specific fusions, and concludes that the claims would have been patentable. At no point during prosecution of the '209 parent or the CIP patent did Cousens et al. present the claims that the Examiner relies on to justify his use of the abandoned '209 application as prior art. Instead, Cousens et al. presented far different claims and then abandoned them in the face of a rejection. This approach is improper under the analysis and holding of *In Re Wertheim.*

The limited circumstances under which the relation-back principle of section 120 may be applied are carefully described in *In re Wertheim*, framing the issue as follows:

> "What patent disclosure, or portion thereof, which has been "carried over" through a chain of applications, may be traced back to an earlier application and given its effective date, and then combined with a secondary reference to reject later filed claims under §§102(e)/103?"

Specifically, the court stated, "an abandoned application by itself can never be a reference." Id. at 535. According to *Wertheim*, the critical legal issue is whether the invention claimed in the subsequent patent finds a supporting disclosure in compliance with section 112, as required by section 120, in the abandoned application so as to entitle that invention to the filing date of the abandoned application for prior art purposes. Id. at 537. If the disclosure of the abandoned application does not fully support a claim in the patent, or if the claims of the subsequent patent derive essential support from new matter added by later continuation-in-part applications, then the abandoned patent application is not effective for prior art purposes under §§102(e) and 103.

This is true even though the disclosed matter in question appeared in the abandoned application and is carried forward into the patent. In this regard, the *Wertheim* court stated:

> We emphasize that the above noted statutes, §§102(e), 120, and 112, speak with reference to some specific claimed subject matter . . .. It is axiomatic in patent law that questions of description, disclosure, enablement, anticipation, and obviousness can only be discussed with reference to a specific claim which identifies "the invention" referred to in the statutes. Thus, the determinative question here is whether the invention claimed in the [subsequently issued patent] finds a supporting disclosure in compliance with §112, as required by §120, in the [remote application] so as to entitle that invention in the [subsequent patent], as "prior art," to the filing date of [the remote application]. Without such support, the invention, and its accompanying disclosure, cannot be regarded as prior art as of that filing date. Id. at 537 (emphasis added).

Furthermore, *Wertheim* criticized and accordingly modified two earlier cases that relied merely on the fact that disclosures in remote or abandoned applications had been "carried over" to later applications. The two modified cases are *In re Switzer*, 166 F. 2d (C.C.P.A. 1948) and *In re Lund*, 376 F. 2d 982 (C.C.P.A. 1967).

In sum the examiner has not analyzed the issue that *Wertheim* requires him to analyze: Does the '209 application support any of the claims issued in the Cousens '180 patent? Hypothetical claims that might have been, but were not, presented are simply irrelevant.

Viewed in that light, it is clear that the '209 application does not support the claims presented in the '180 patent (which were quite different from the unpatentable claims presented in the '209 application). It is improper under *Wertheim* to rely on the abandoned '209 application in these circumstances.

Without the '209 application, the rejection must be withdrawn

b. Even if the answer to question B.2.a., above is "yes", has the Examiner provided a basis in fact and/or technical reasoning to reasonably support the determination that the Cousens fusion peptides inherently possess each feature specified in claim 47?

As noted, claim 47 requires that the hinge sequence include at least two amino acids defining a secondary structure that promote cleavage by said cleavage agents at said cleavage site. Applicants point out that the two amino acids cannot be part of the cleavage site itself or of

the leader sequence, each of which is recited as a separate claim element from the hinge region that contains the two required amino acids.

What then is the technical reasoning that the Examiner uses to support the idea that the two prior art fusion peptides contain: a) a leader sequence; b) a cleavage site; and c) a hinge that includes at least two amino acids that define a secondary structure that promotes cleavage by CNBr (the cleavage agent that Cousens uses)? The analysis in the final rejection references item 5 in paper 31 (the non-final rejection). While item 5 contains a lengthy discussion of the issues that were being raised at the time, the only part of item 5 dealing with this key issue is at page 7,

> The text in lines 23 to 35 in column 4 of the Cousens et al. patent shows that a linker of at least two amino acids in length and which is composed of only serine and threonine residues is expected to be flexible.

The Examiner has failed to explain how the referenced text bears on the issue at hand. The issue is whether the two Cousens fusion peptides inherently satisfy all the claim limitations. The above quoted statement references the following text from the Cousens CIP application, which is not itself prior art. That text is reproduced below in its entirety.

> The "hinge" amino acid sequence could be of variable length and may contain any amino acid side chains so long as the side chains do not interfere with the mode of action employed to break at the cleavable site or with required interactions in either fused polypeptide, such as ionic, hydrophobic, or hydrogen bonding. Preferably the amino acids comprising the hinge would have side chains that are neutral and either polar or non-polar and may include one or more prolines. The hinge region will have at least one amino acid and may have 20 or more amino acids, usually not more than 15 amino acids, particularly the non-polar amino acids G, A, P, V, I, L, and the neutral polar amino acids, N, Q, S, and T.
>
> Exemplary hinge sequences may be, but are not limited to: N-S; Q-A; N-S-G-S-P; A-A-S-T-P; N-S-G-P-T-P-P-S-P-G-S-P; S-S-P-G-A.

There is no reason to think that the above text is intended to characterize the two specific fusion molecules at issue here. This becomes especially clear when one considers the "spacers" of the concrete fusion molecules described at column 8, lines 13-36 of the Cousens '180 patent as KRSTS (for pYPKI2) and KR$(ST)_2$S (for pYSI2). These spacers are not given as preferred or even suitable hinge sequences at column 4, lines 36-38 of the Cousens '180 patent, leading to the conclusion that the concrete spacers described for these molecules are not what is meant by

"hinge". Indeed, the most reasonable interpretation of the newly added discussion of hinges at column 4, lines 36-38 of the Cousens '180 patent is that the concept of "hinges" was added in view of specific molecules and sequences that were also added in the CIP and that concept does not apply at all to the molecules and sequences in the parent '209 application. Nevertheless, the Examiner concludes,

> The text in lines 23-35 in column 4 of the Cousens et al. patent shows that a linker of at least two amino acids in length and which is composed of only serine and threonine residues is expected to be flexible.

Is the Examiner saying that each and every linker containing an S-T pair is flexible? Certainly the Cousens CIP patent does not go that far.

To bolster the argument and perhaps to equate "flexibility" (which is not recited in the claim) with the claim phrase, "**promote cleavage by said cleavage agents at said cleavage site**", the Examiner cites page 19 of applicants' specification,

> The text in the first paragraph on page 19 of the instant specification indicates that such a linker [i.e., a linker of at least two amino acids in length and which is composed of only serine and threonine residues] would be expected to be flexible and to facilitate proteolytic cleavage of a fusion protein if positioned next to an endopeptidase cleavage site, as was the linker of Cousens et al. Therefore the instant specification supports a conclusion that those two fusion proteins of Cousens et al. inherently meet all of the limitations of the instant claim.

Let's look at the first paragraph of page 19 of the instant specification. It says,

> Particularly when the preselected cleavage agent is an endopeptidase, it is important that the hinge region be soluble in aqueous environments. Amino acids having charged side groups and hydrophilic properties are included in the hinge to promote solubility. These include the anionic residues Glu [E] and Asp [D], and the neutral hydrophilic residues Ser [S] and Thr [T].

So the specification recommends charged residues E and D; Cousens recommends non-polar residues V and L. Both also list uncharged residues S and T that are polar because they contain an –OH side chain. Apparently the Examiner would draw the conclusion that each and every sequence containing residues that are charged or that are non-polar or that are uncharged but polar must satisfy the claim limitation. The Examiner gives no explanation for how the above-cited Cousens text and the text at page 19 of the specification supports his finding that the two

specific Cousens fusion peptides include a hinge that has **"...at least two amino acids defining a secondary structure which promote cleavage by said cleavage agents at said cleavage site."**

Most of the Cousens CIP text (remember that this text is not prior art) cuts against the Examiner's conclusion. The cited Cousens CIP text recommends non-polar amino acids G, A, P, V, I, L, which are not included in the hinge of the two prior art fusion peptides. It of course also recommends the neutral polar amino acids, N, Q, S, and T, thus listing a total of 10 of the 22 possible naturally occurring amino acids. When added to the two charged amino acid residues mentioned at page 19 of the Applicants' specification (G and E), it appears that the Examiner would find inherent anticipation in any sequence containing any of the 12 listed amino acid residues at two or more positions. There is no basis for this sweeping conclusion. The vast majority of a random set of 5-mers would contain one of those twelve amino acids at two or more positions, yet there is no reason to think all such 5-mers would exhibit the claimed properties. Nor does it necessarily follow that every peptide exhibiting "hinge" properties of Cousens would satisfy the claim limitations. As noted, the Cousens prior art fusion molecules do not contain any of the "exemplary" hinge sequences specified in the text of the CIP patent at column 4, quoted above.

After the attempt to rely on the non-art in the Cousens CIP application and on the Applicants' specification to show inherency, the Examiner then generalizes in the extreme, citing Lehninger for general principals of peptide α-helix formation. Apparently the examiner relies on Table 6-1 of Lehninger, which lists Ser (S) and Thr (T) as "destabilizing" the α-helix. From that table, the examiner concludes that the specific sequence in the Cousens prior art fusion peptides must be (inherently are) "flexible" because those sequences include an S-T pair. A second leap of faith is that this "flexibility" equates to the claimed characteristic. How does the Examiner explain that the key Cousens CIP statement quoted above – the very statement that the Examiner relies on to show inherency -- advocates just the opposite of the conclusion he draws from the Lehninger Table 6-1? Cousins prefer the inclusion of non-polar amino acids such as Val (V) and Leu (L), peptides that Lehninger's Table 6-1 lists as <u>stabilizing</u> formation of an α-helix.

So which is it? Do all peptides that include non-polar amino acids such as V and L inherently satisfy the claims, as the Examiner suggests in citing the Cousens CIP? Or do all

peptides that avoid such non-polar amino acids inherently satisfy the claims, as the Examiner suggests in citing Lehninger? Or does the Examiner conclude that all peptides inherently satisfy the claims, regardless of composition?

The fact is, the Examiner has not provided a reasonable basis to conclude that the two prior art Cousens fusion peptides inherently include the claim limitation at issue. The Examiner relies heavily on the S-T pairing in the prior art Cousens et al. fusion peptides, but there is no reason to think that S-T pairing, in fact and automatically, provides the claimed characteristic in either of the two prior art Cousens fusion molecules, any more than any of a large number of pairings, such as V-L pairing, would do.

The anticipation rejection must be withdrawn.

C. Obviousness of claims 60 and 61 based on Cousens (U.S. 4,751,180) and Löfdahl et al (WO84/03103) and Lehninger, further in view of Cohen (U.S. 4,743,679)

For all of the reasons given above, the reliance on Cousens is improper and this rejection must be withdrawn.

Even if the content of the Cousens '209 application is available as prior art, the rejection must be withdrawn for all of the reasons given above.

In addition, it is particularly egregious that the Examiner's obviousness rejection assumes that the art appreciated and understood the properties of the two Cousens fusion peptides that the Examiner characterizes as "inherent" in those peptides. Quite apart from the question presented above regarding anticipation, an obviousness rejection must be limited to the information expressed in the art. Inherent but unappreciated properties of prior art compositions cannot form the basis for an obviousness rejection. For all of the reasons given above, the art did not attribute the claimed characteristics to the two Cousens fusion peptides, and the proposed combination of references is does not provide any basis to alter the prior art fusion peptides so as to include the claimed elements (claim 60—a Glu residue in the cleavage site; claim 61 – site cleaved by *S. aureus* V-8 protease). On what prior art disclosure does the Examiner find a motivation to combine reference to produce the invention of claims 60 and 61? Certainly the referenced paragraph 6 in paper 31 provides no basis at all. The Examiner has not explained how the art

would have been motivated to combine the disclosure in the '209 application (EXCLUDING THE LATER CIP MATERIAL) with Cohen's disclosure concerning *S. aureus* V-8 protease.

The obviousness rejection must be withdrawn.

Applicant asks that all claims be allowed. Enclosed are an $18.00 check for excess claim fees and a $1440.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 9/9/02

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